Nuevos fármacos para el tratamiento del VHD

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Disclosures

Speaker and Advisor of Abbvie, and Gilead

Chronic hepatitis delta: heterogeneous course

- Chronic hepatitis delta is associated with:
  - Accelerated fibrosis progression
  - Increased risk of HCC and early decompensation

Rizzetto M. J Hepatol 2009; 50: 1043-50

- Asymptomatic HDV-HBV carriers may also exist

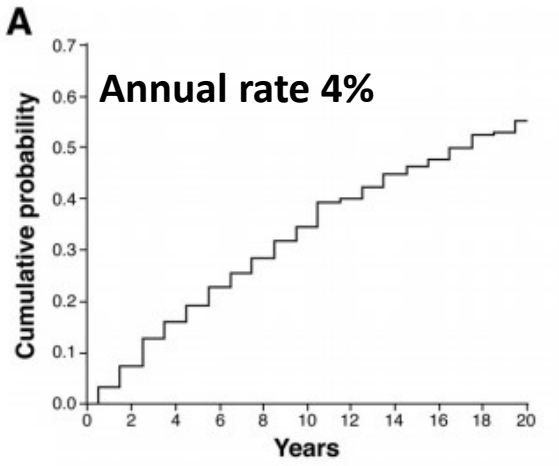
Rizzetto M. J Hepatol 2009; 50: 1043-50;

Hadziyannis SJ et al. Prog Clin Biol Res 1987; 234: 181–202.

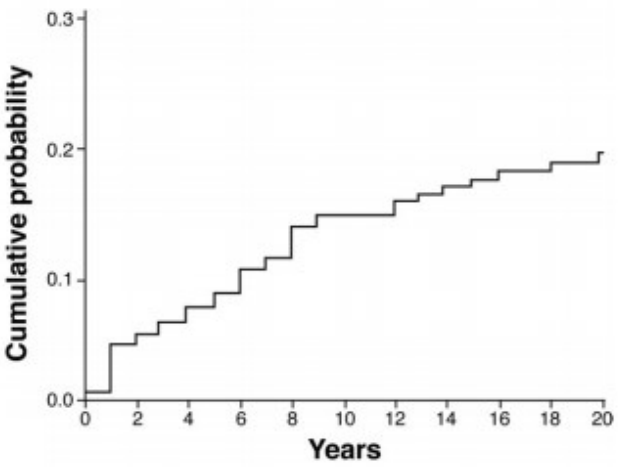
Probability of developing clinical events in chronic hepatitis delta

Mean follow-up of 19 years

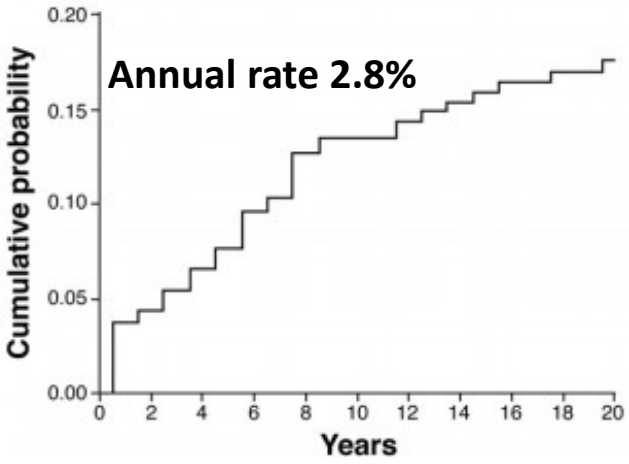
Cirrhosis
(N=299)



Decompensation
(N=186)



Hepatocelullar Carcinoma
(N=299)



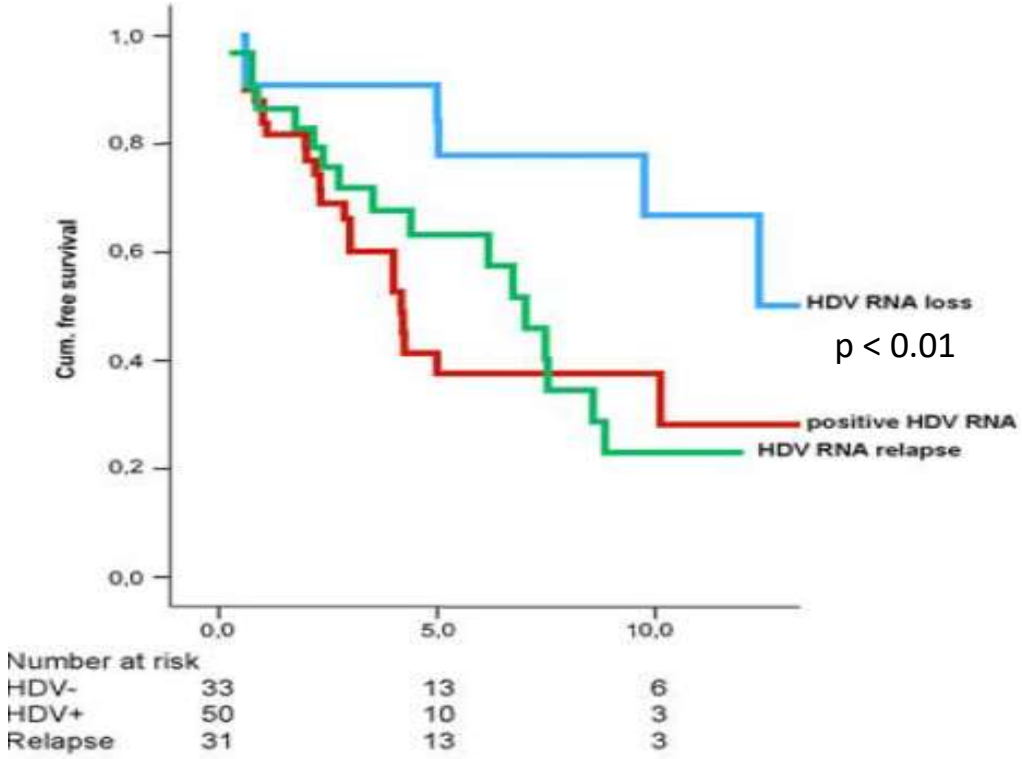
Factors associated with worse outcome in chronic hepatitis Delta

Persistent HDV RNA

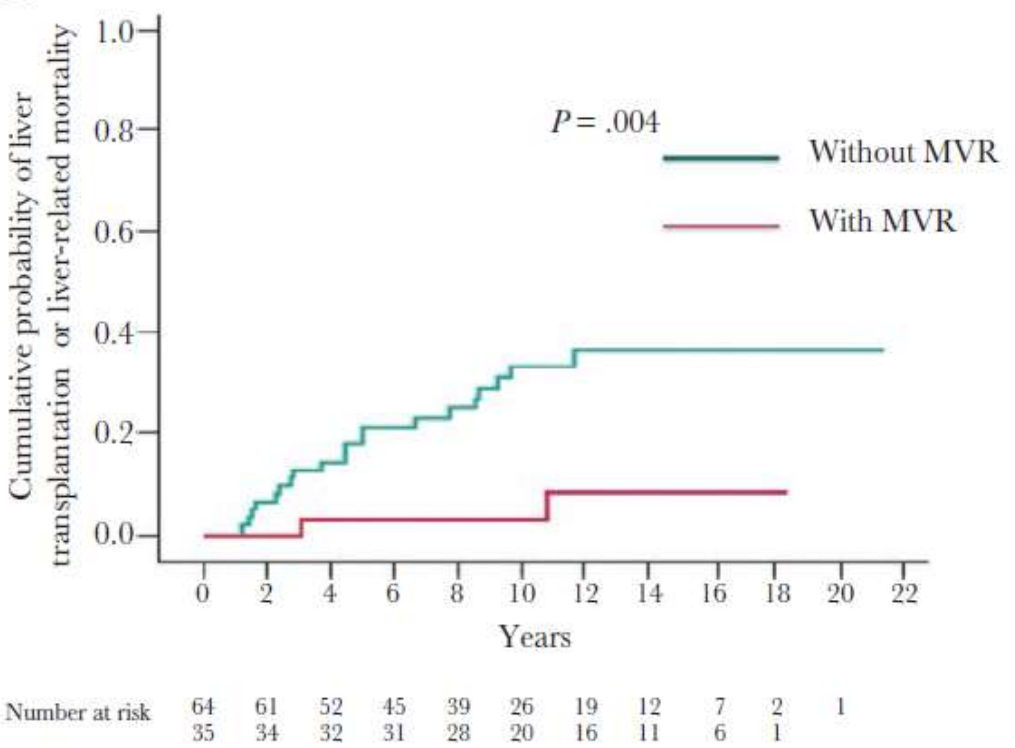
Male gender
Cirrhosis at diagnosis
Lack of antiviral therapy

Romeo F et al Gastroenterology 2009;136:1629-1638; Niro GA, et al. J Hepatol. 2010;53(5):834-40

Long-term survival in patients with undetectable HDV RNA



Wranke A et al. Hepatology 2017;65:414-425

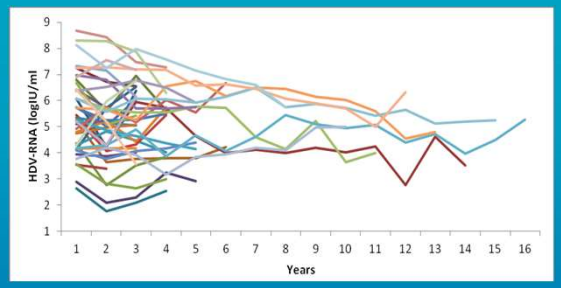


Yurdaydin C et al. J Infect Dis. 2018;217:1184-1192

Do chronic hepatitis D patients show spontaneous declines in HDV-RNA levels?

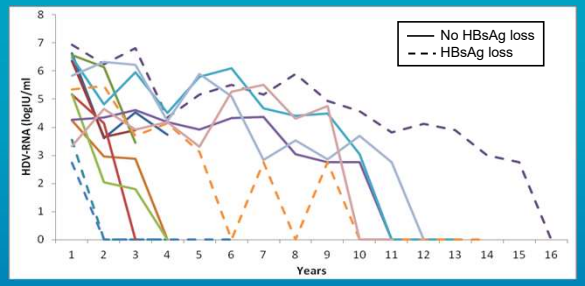
56 included patients

42 show <2 log10 HDV-RNA decline overtime



0 become HDV-RNA undetectable

14 show ≥2 log10 HDV-RNA decline overtime



11 become HDV-RNA undetectable

Outcomes

Patients with ≥2 log10 HDV-RNA decline have more chance of:

HBsAg decline
ALT normalization
HDV-RNA undetectability

These findings may have implications for the design of studies with new therapies for chronic hepatitis D

Palom, et al. *Aliment. Pharmacol. Ther.*

AP&T

EASL and AASLD recommendations for therapy of Chronic Hepatitis Delta

EASL Recommendations

HDV co-infected patients
Recommendations

- PegIFNα for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease (Evidence level I, grade of recommendation 1).
- In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1).
- PegIFNα treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated (Evidence level II-2, grade of recommendation 2).

EASL Guidelines 2017

AASLD Recommendations

Peg-IFN-α for 12 months is the recommended therapy for those with elevated HDV-RNA levels and ALT elevation.
If HBV-DNA levels are elevated, concurrent therapy with NA using preferred drugs (entecavir, TDF, or TAF) is indicated.
Assessment of HDV-RNA is warranted if ALT elevation occurs following treatment because of the high rates of relapse.
Given the limited efficacy of current therapies, it is reasonable to refer patients to specialized centers that offer access to experimental therapies for HDV.

Terrault N et al Hepatology 2018

48 wks course of PegIFN+ADV vs PegIFN vs ADV in Chronic Hepatitis Delta

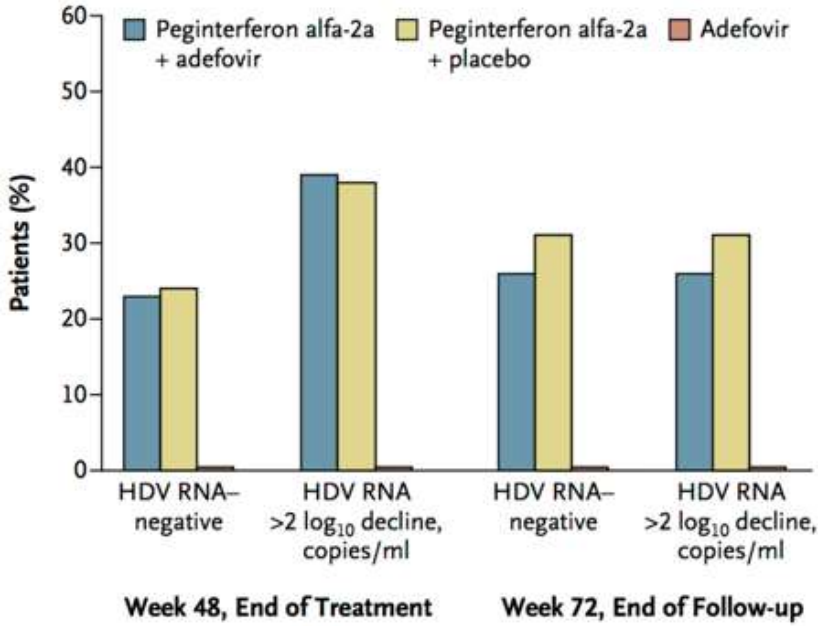
N=90
Chronic Hepatitis Delta

PEG-IFNα-2a (180 µg/wks) + ADV 10 mg/day (n = 31)

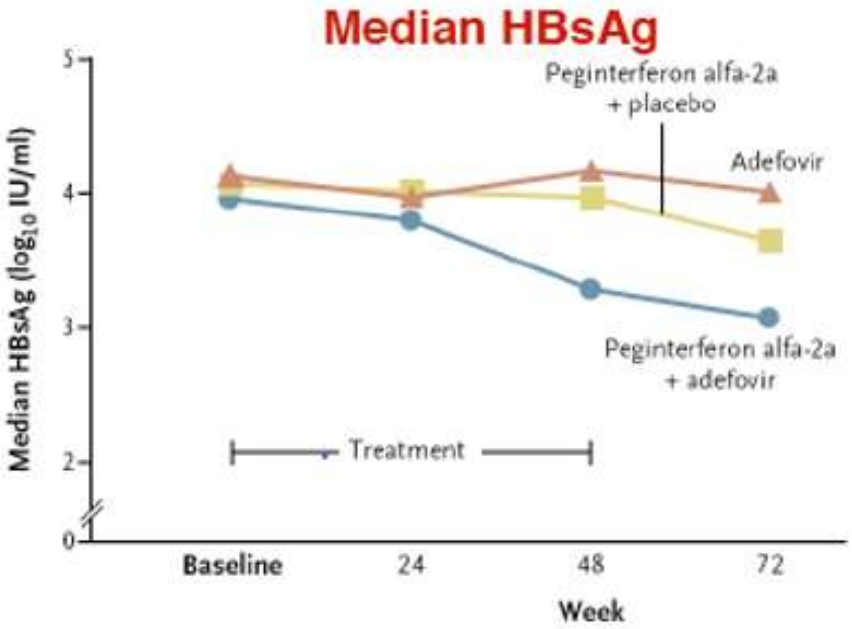
PEG-IFNα-2a (180 µg/wks) + placebo (n = 29)

ADV 10 mg/day (n = 30)

Primary End-Point: HDV RNA undetectable and Normal ALT at week 48



All HDV GT 1
14-24% cirrhosis

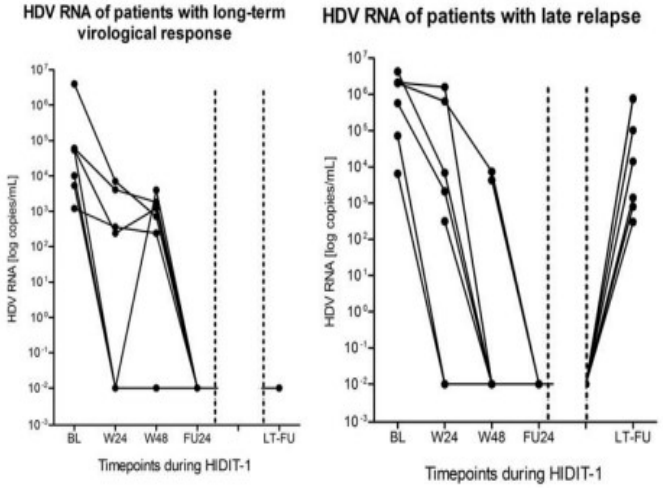


HBsAg loss: 2 patients treated with PegIFN/ADV

Wedemeyer H. et al, N Eng J Med 2011;364:322-331

Changes in Hepatitis Delta Viremia after treatment discontinuation

- Early (24 weeks post-treatment)
  - Viral response
    - HDV RNA became undetectable in 3 patients in each groug
  - Relapse
    - PegIFN/ADV 1/7 (14%)
    - PegIFN 1/7 (14%)
- Late (5 years follow-up)
  - 9/16 (56%) patients with viral response post-treatment week 24 tested HDV RNA Positive



Heidrich et al. Hepatology 2014

Bulevirtide (Myrcludex B)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4.1 Therapeutic indications

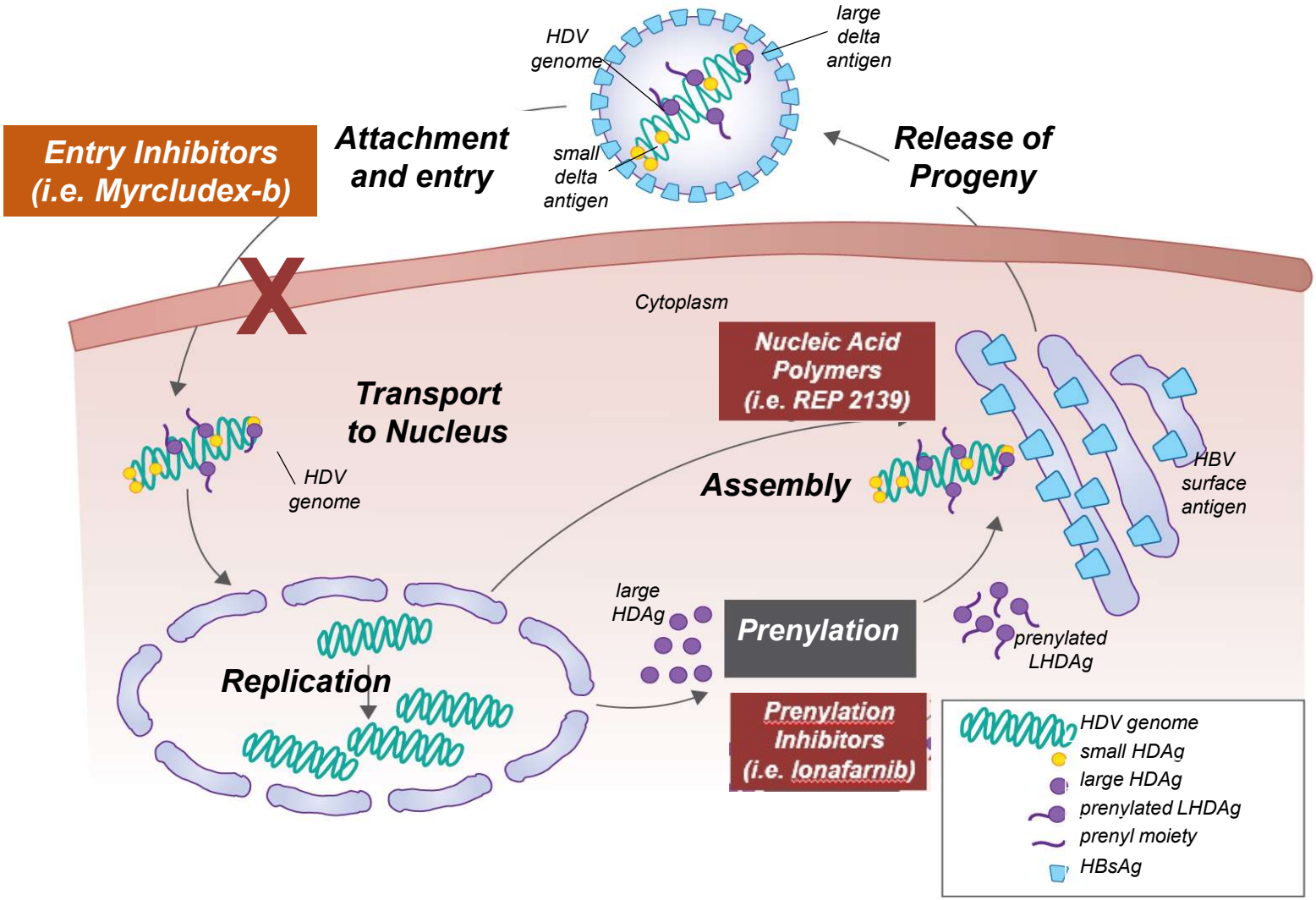
Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

4.2 Posology and method of administration

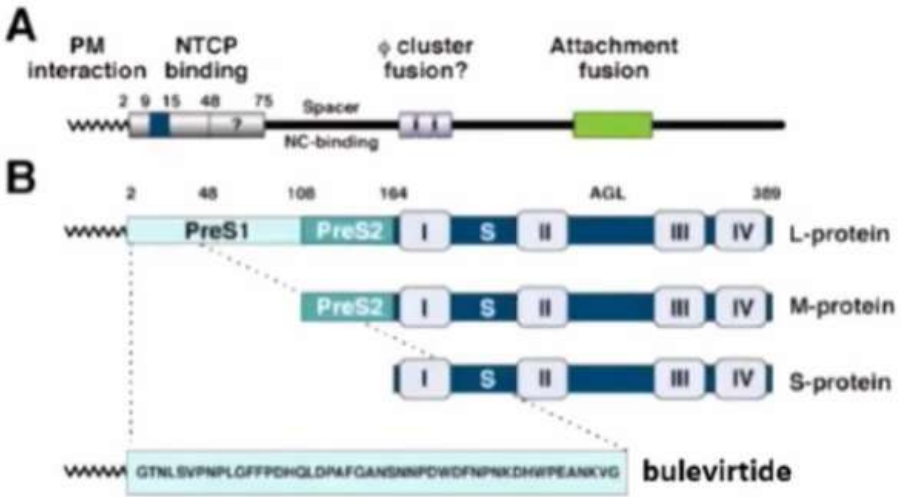
Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection.

Bulevirtide should be administered at 2 mg once daily (every 24 h ± 4 h) by subcutaneous injection as monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying HBV infection.

The HDV Life Cycle



Bulevirtide (Hepcludex®)



Urban et al., Gastroenterology 2014;147:48-64

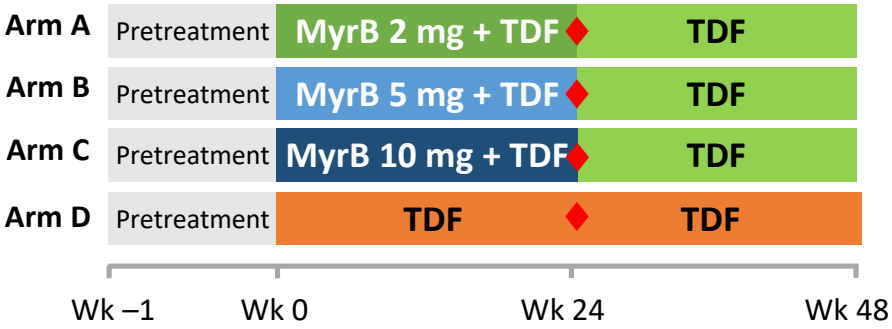
- Specifically **binds to sodium taurocholate co-transporting polypeptide (NTCP)** at the basolateral membrane of differentiated hepatocytes (*Ni et al., Gastroenterology. 2014;146:1070-1083; Urban et al., Gastroenterology. 2014;147:48-64*).
- Shows strong inhibitory potential for HBV/HDV infection (IC_{50} ca 80 pM in PHH) (*Schulze et al., J. Virology. 2010;84:1989-2000*).
- Exclusively targets parenchymal liver cells (*Meier et al., Hepatology. 2013;58:31-42*).

- Has been **dosed to >600** hepatitis B and D patients and healthy subjects
- Bulevirtide monotherapy **induced HDV RNA declines and improved ALT levels** in hepatitis D patients in the MYR202 trial (24 weeks of treatment) *(Wedemeyer et al., EASL 2018)*
- Combination of 2mg or 5mg **bulevirtide with PEG-IFNα induced synergistic effects** *(Wedemeyer et al., EASL 2019)*
- **2mg Bulevirtide (Hepcludex®) has been approved** for the treatment of chronic HDV infection in adult patients with compensated liver disease in Europe.

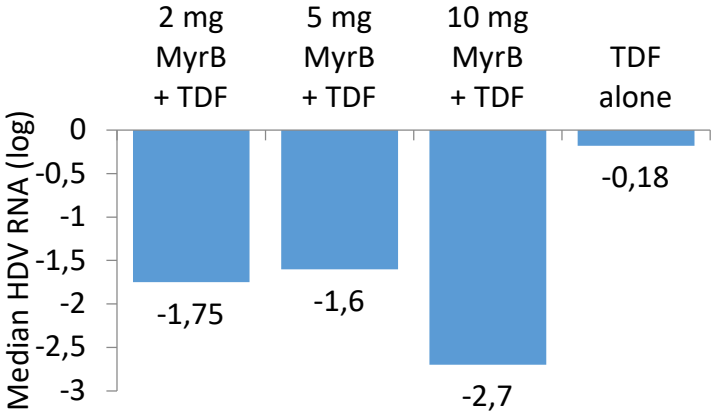
Final results of a multicenter, open-label Phase 2b trial to assess safety and efficacy of Bulevirtide + TDF in patients CHD (MYR 202)

Study design

- 120 patients randomized into 4 treatment arms in a ratio of 1:1:1:1
  - 30 patients per arm; 50% of patients were cirrhotic
- Myrcludex B was self administered by patients SC QD
- All patients received TDF (oral QD) during entire study period
- Primary endpoint: HDV RNA decline by ≥2 $\log_{10}$ from BL to Wk 24

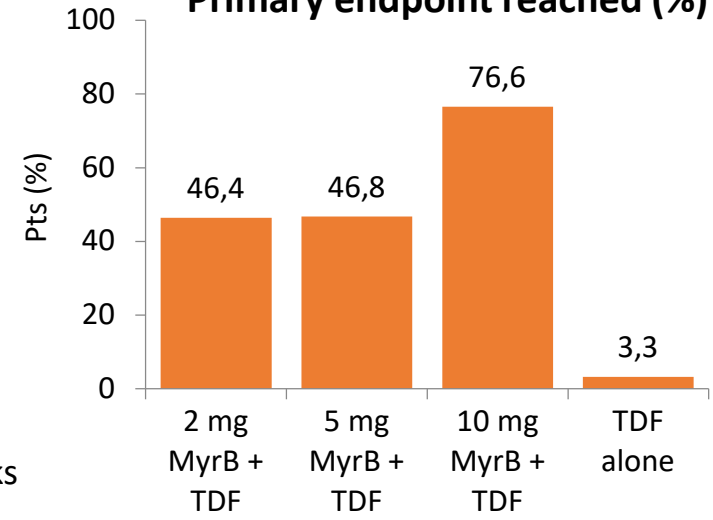


Median HDV RNA (24 wks)

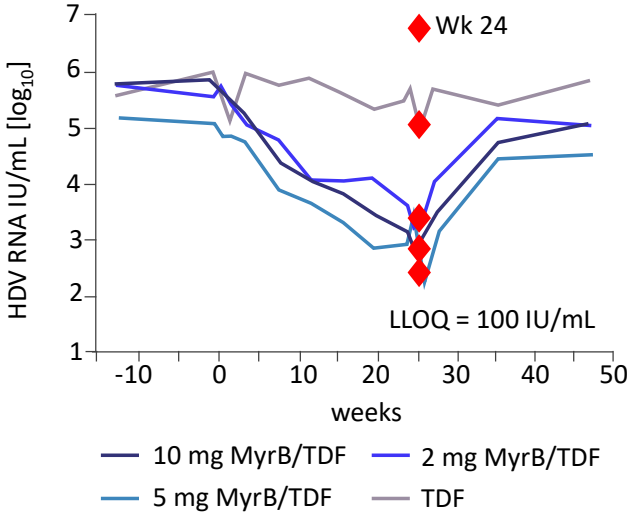


- HDV RNA levels were still declining at 24 weeks

Primary endpoint reached (%)



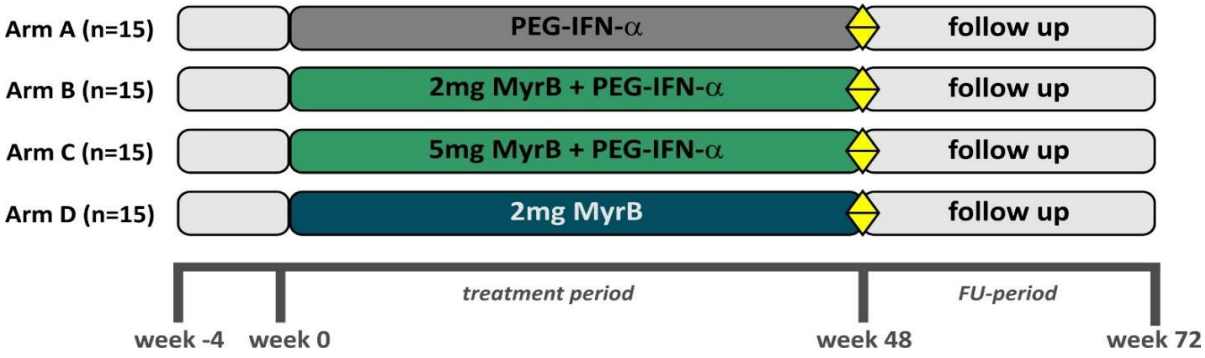
Virologic response HDV RNA



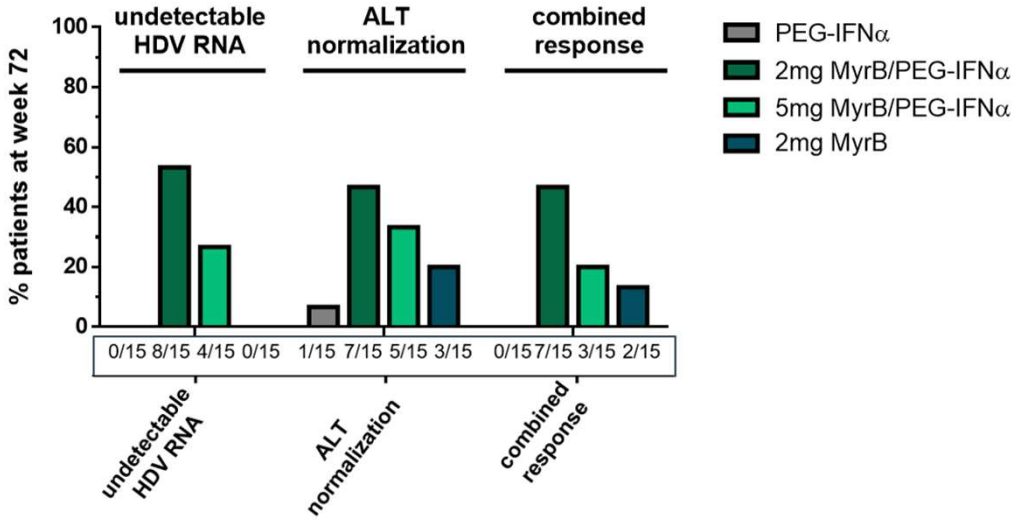
Bulevirtide with PEG-interferon α 2a: Safety and efficacy in patients with CHD in a phase 2 trial (MYR203)

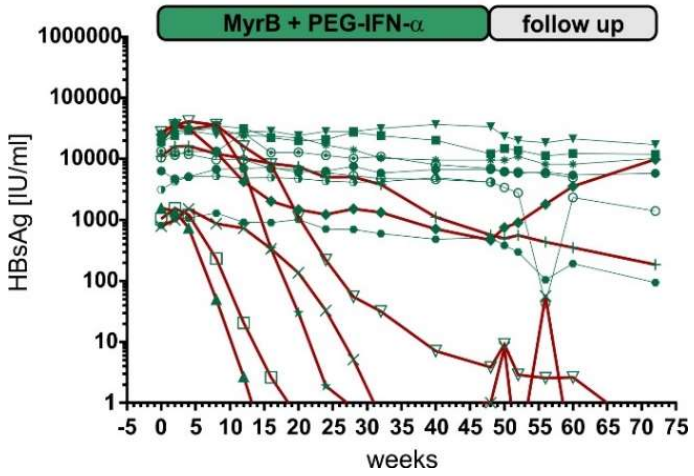
60 patients CHD randomized

Primary endpoint: HDV RNA undetectable at Week 24 of follow up



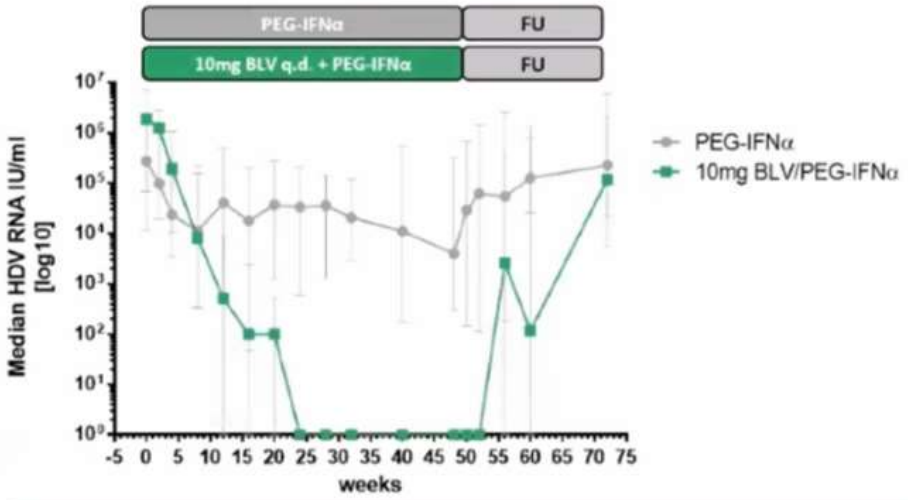
2 mg MyrB plus PEG-IFNα achieved HDV RNA undetectable and HBsAg loss in 40%



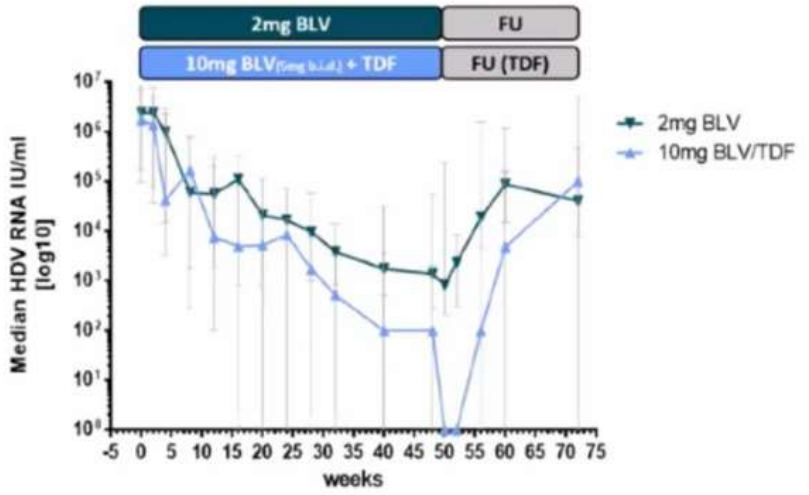


Wedemeyer H, et al. ILC 2019; GS-13

MYR 203 extension study



Virological response: week 72	Primary endpoint: undetectable HDV RNA	>2log$_{10}$ reduction or undetectable HDV RNA
PEG-IFNα	0.0%	0.0%
2mg BLV + PEG-IFNα	53.3%	73.3%
5mg BLV + PEG-IFNα	26.7%	46.7%
10mg BLV + PEG-IFNα	6.7%	33.3%

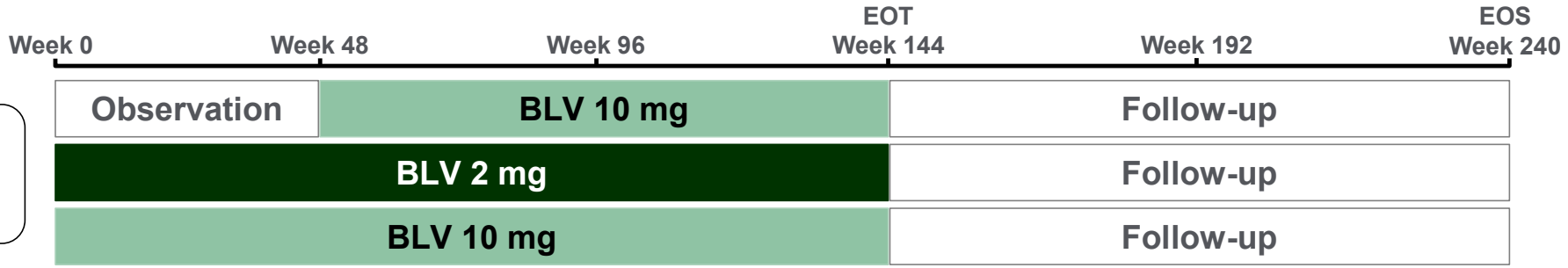


Virological response: week 72	Primary endpoint: undetectable HDV RNA	>2log$_{10}$ reduction or undetectable HDV RNA
2mg BLV	6.7%	33.3%
10mg BLV + TDF	33.3%	46.7%

MYR301 Study Design

‡

Ongoing, Phase 3, randomized, multi-center, open-label study



Key Inclusion Criteria
- Anti-HDV+ for ≥6 months
- Positive HDV RNA
- ALT ≥1 ULN but <10x ULN

Primary endpoint:
- Combined response HDV RNA undetectable *or* decrease by ≥2 log IU/mL from baseline and ALT normalization (week 48)

Secondary endpoints:
- Undetectable HDV RNA
- ALT normalization
- HDV RNA undetectable 24 weeks after EOT
- HDV RNA undetectable 48 weeks after EOT
- Change in liver stiffness

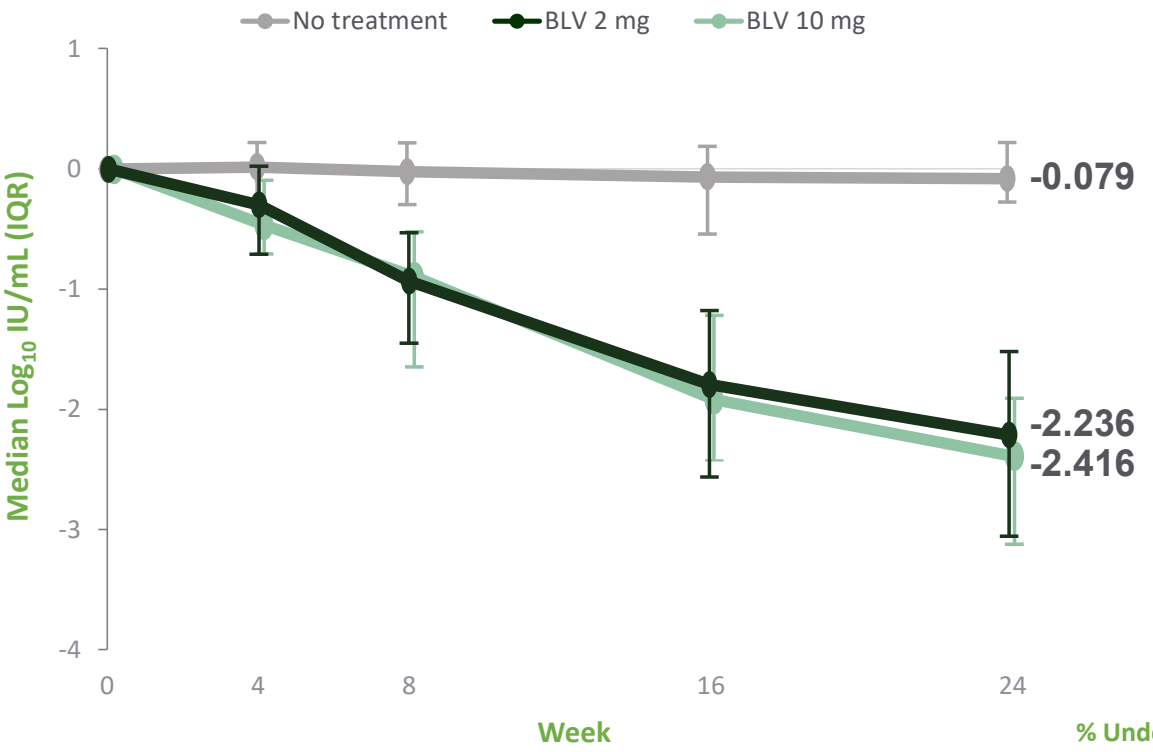
ALT, alanine aminotransferase; BLV, bulevirtide; EOS, end of study; EOT, end of treatment; HDV, hepatitis D virus.

References: 1. Gilead, Data on File. **2.** Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03852719

MYR301 Phase 3 Study for Chronic Therapy

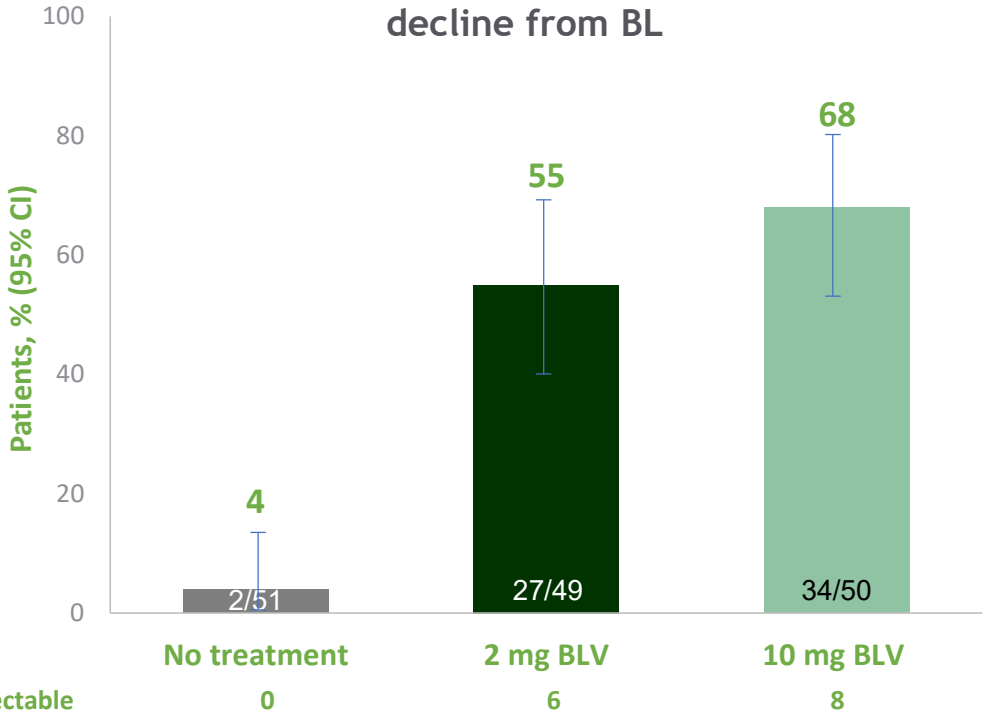
Virologic Response Through 24 Weeks

HDV RNA Levels Over Time



Virologic Response at Week 24

Undetectable HDV RNA or ≥2 log IU/mL decline from BL

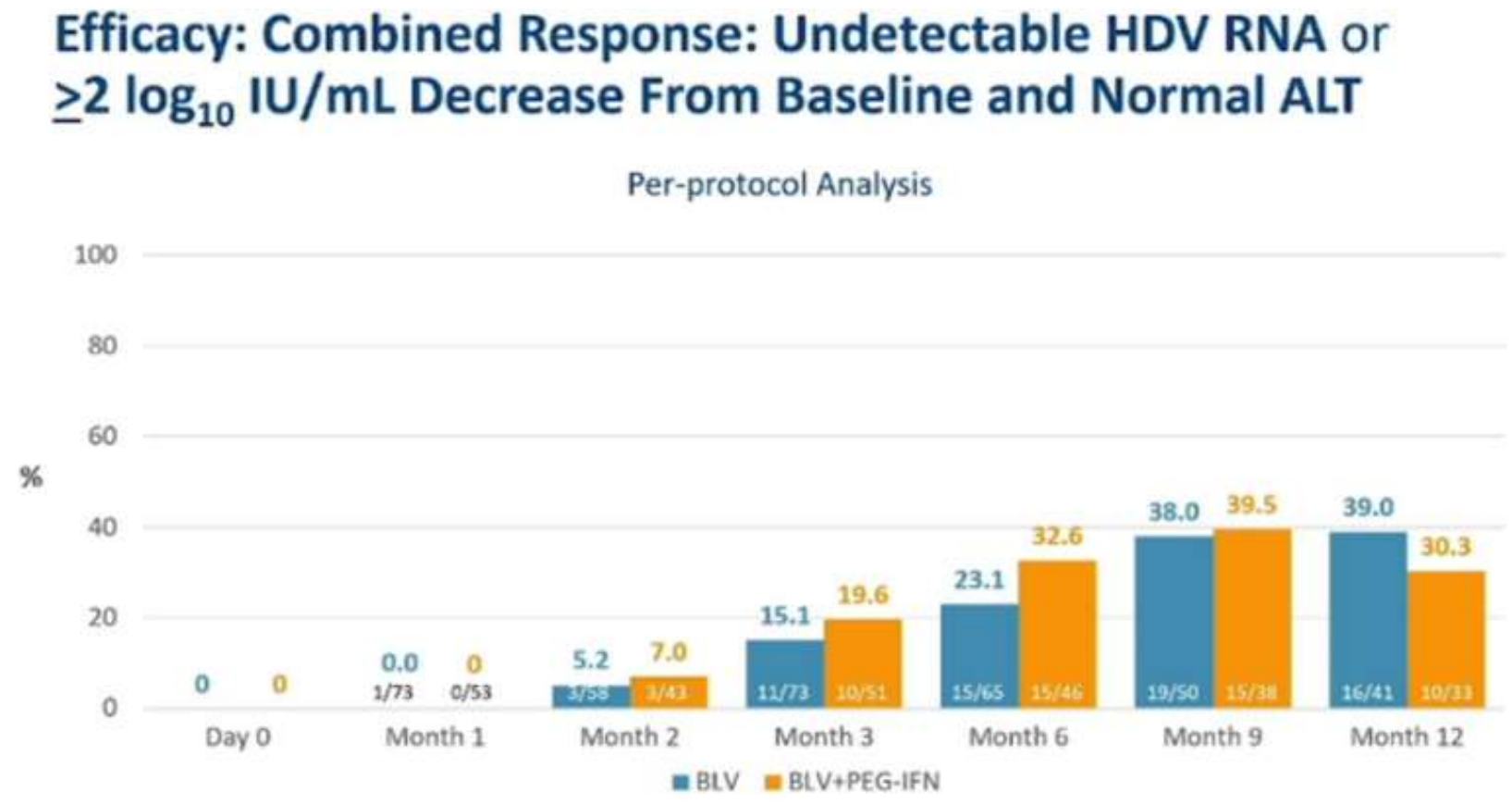


BLV led to similar rates of HDV RNA decline with 2 or 10 mg over 24 weeks of treatment

BLV monotherapy was associated with significant HDV RNA declines

[17] Undetectable HDV RNA defined as below lower limit of detection (6 IU/mL); IQR=interquartile range; CI=confidence interval
Wedemeyer H, et al. EASL 2021. #2730

SAFETY AND EFFICACY OF 2mg BULEVIRTIDE IN PATIENTS WITH CHRONIC HBV/HDV CO-INFECTION. FIRST REAL-WORLD RESULTS (FRENCH EARLY ACCESS PROGRAM)



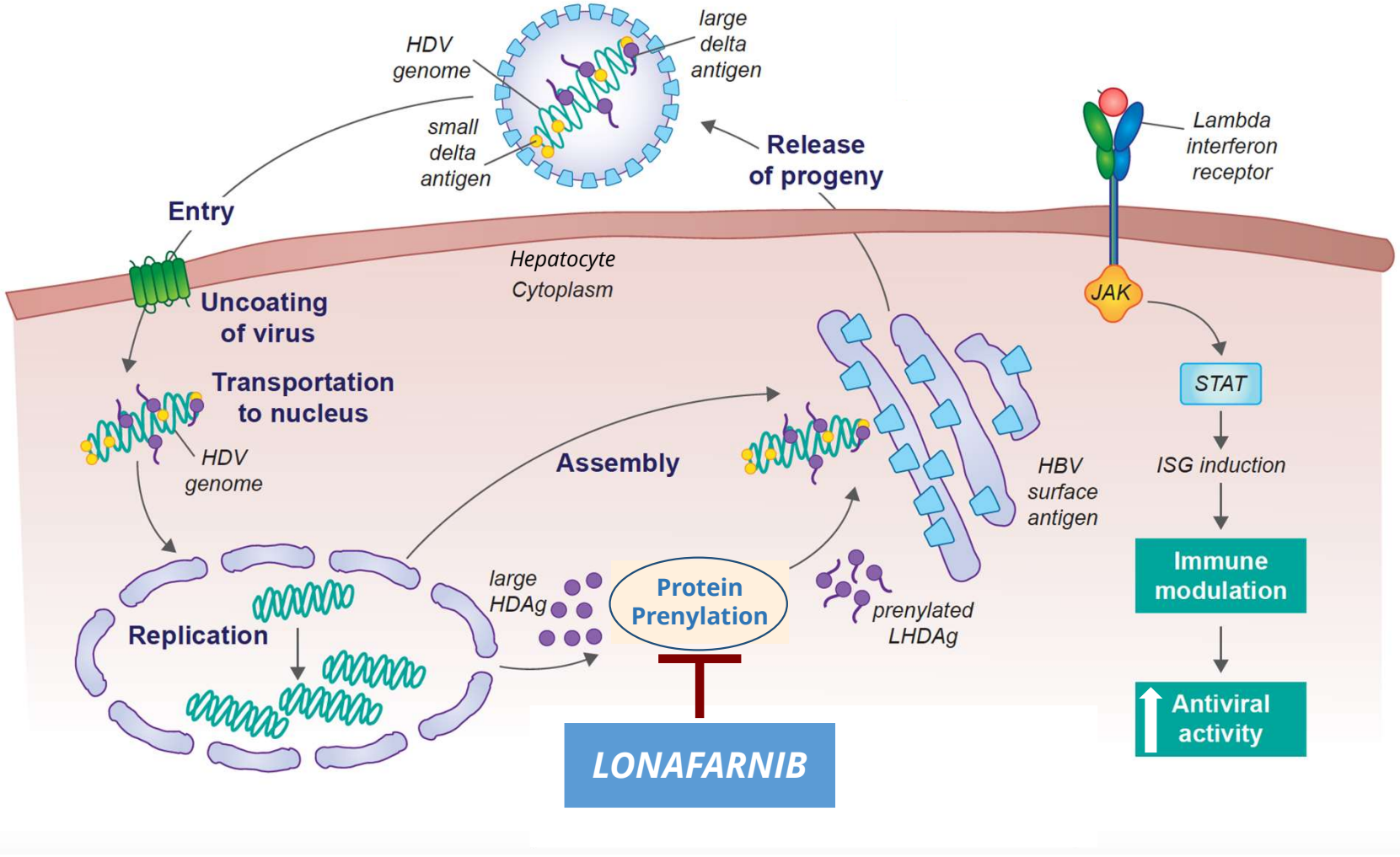
Normal ALT defined as < 40 IU/L. missing does not equal failure. Study not powered to compare the two treatment regimens

De Ledinghen V et al AASLD 2021

Bulevirtide: summary

1. Bulevirtide (Hepcludex®) 2mg s/c has been approved for the treatment of chronic HDV infection in adult patients with compensated liver disease in Europe.
2. Strong antiviral synergism of bulevirtide 2mg s/c in combination with PEG-IFNα.
3. Bulevirtide high-dose therapy was safe and well tolerated.
4. Ongoing studies in HDV infection (MYR301 and MYR204 studies).

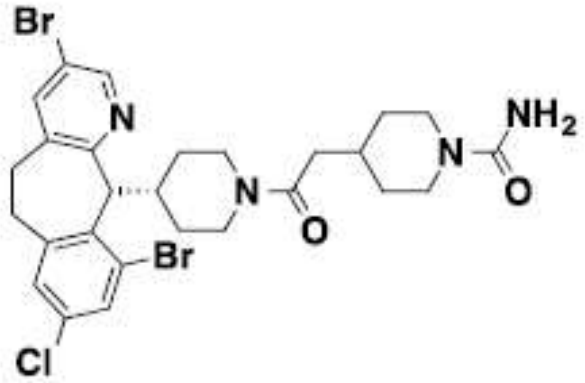
Sites of investigative drug targets



*Nuc = HBV nucleoside or nucleotide Rx. All patients will be on background HBV nuc therapy (Tenofovir or Entecavir)

LONAFARNIB FOR HDV

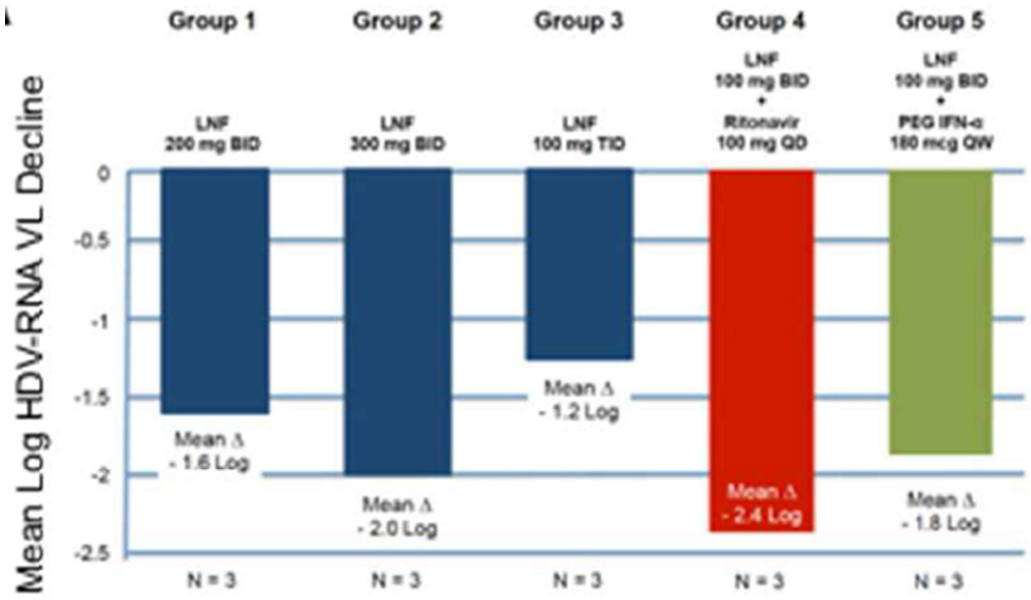
Well-characterized Clinical Stage Lead Compound

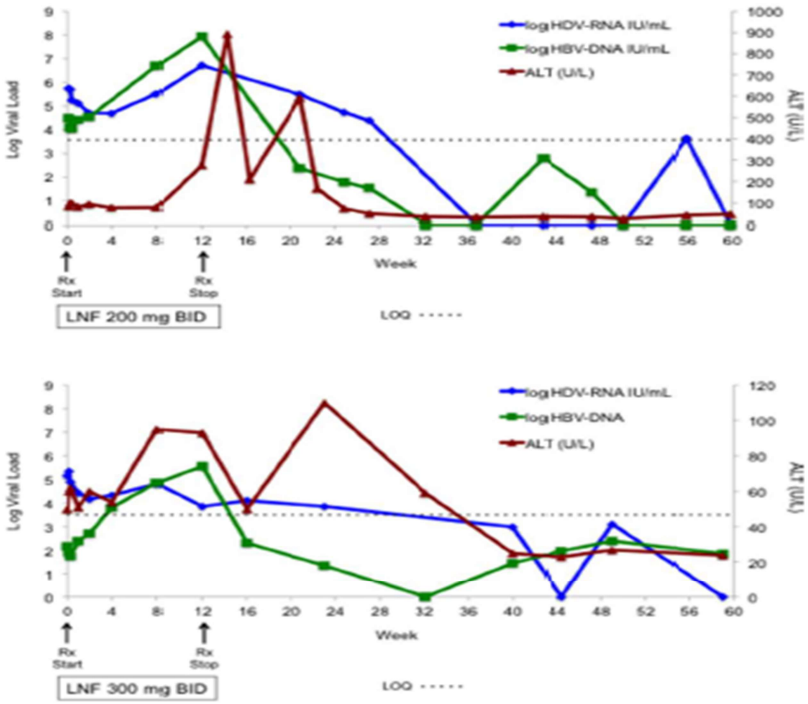


- Small molecule, oral, prenylation inhibitor
- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck (Schering)
  - Dose limiting toxicity is GI (class effect)
- Over 120 HDV patients dosed across international sites
- HDV Orphan Designation in US & EU, Fast Track in US
- Patent issued allowing broad range of lonafarnib + ritonavir doses and durations
- Prenylation is a host target; potential barrier to resistance

Lonafarnib with Ritonavir in Patients with Hepatitis Delta

Phase 2 LOWR-1 Study:Open label study of 15 subjects with CHD treated for 12 weeks with LNF ± Ritonavir





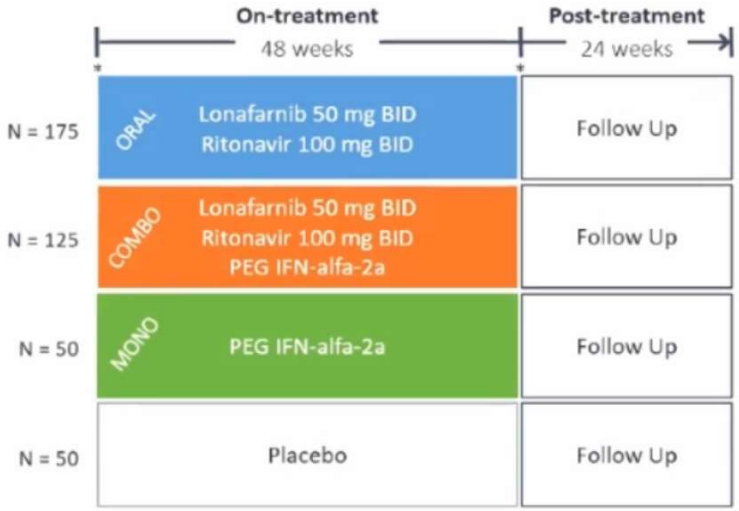
Ritonavir reduces GI side effects

LOWR HDV (LOnafarnib With Ritonavir)

Yurdaydin C et al .Hepatology 2018

Phase 3 Global Study

D-LIVR



Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA

+

Normalization of ALT

Secondary Endpoint at Week 48

Histologic improvement

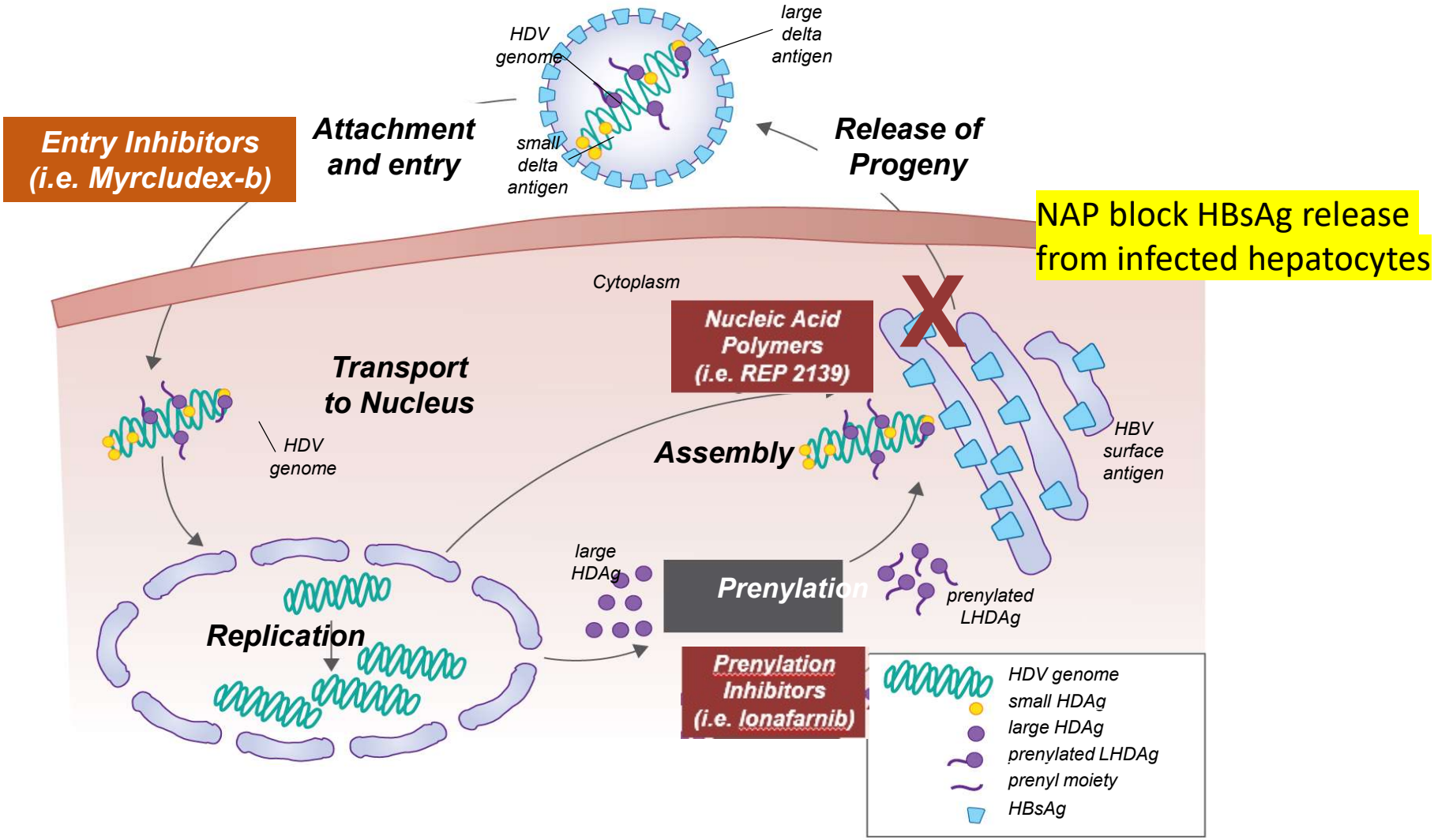
Improvement of fibrosis

* biopsy

All patients will be maintained on background HBV nucleoside therapy.

Superiority over PEG IFN-alfa-2a not required.

Sites of investigative drug targets



Summary

- Hepatitis Delta represents the most severe form of chronic hepatitis
- HDV is underdiagnosed and HDV screening should be performed in all HBsAg-positive patients
- IFN is the recommended therapy but has limited efficacy in patients with CHD and non negligible side effects
- Bulevirtide is recently approved drug to treat CHD with compensated liver disease
- Drugs in development for HDV include prenylation inhibitors and HBsAg secretion inhibitorsand also drugs in development for CHB